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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1628	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,12,14,15 and 17-27* is/are pending in the application.

4a) Of the above claim(s) *6-10,14,15 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,12,17 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This application contains claims 6-10, 14-15 and 18-26, drawn to an invention nonelected with traverse in the reply filed on 7/7/2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments

2. Applicants' arguments, filed 5/4/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Applicant's arguments with respect to the rejection under 35 USC 103 have been fully considered but they are not persuasive:

Claims 1-2, 5, 12, 17 and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over DeLongueville et al. (WO 02/47689 A2; cited in a prior Office Action); Gilliland et al. (Gilliland 1) ("The bactericidal activity of a methyl and propyl parabens combination: isothermal and non-isothermal studies"; 1992; Journal of Applied Bacteriology; 72: 252-257; cited in a prior Office Action); Gilliland et al. (Gilliland 2) ("Kinetic evaluation of claimed synergistic paraben combinations using a factorial

design"; 1992; Journal of Applied Bacteriology; 72: 258-261; cited in a prior Office Action); and Doron et al. ("Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus"; 2001 International Journal of Antimicrobial Agents; 18: 575-578; cited in a prior Office Action); in view of Routledge et al. ("Some Alkyl Hydroxy Benzoate Preservatives (Parabens) Are Estrogenic"; 1998; Toxicology and Applied Pharmacology; 153: 12-19; cited in a prior Office Action).

The rejection is maintained for the reasons of record.

Applicant argues that the present invention is based on the surprising finding that the active substances, including levocertirizine, possess a preservative effect in aqueous solutions; that an unexpected finding that a pharmaceutical composition comprising the active substance and a reduced amount of preservatives is stable, resistant to microbial contamination, for a long period of time; that it is wholly unexpected that a levocetirizine composition could be made with both a low concentration of parabens and an MP/PP ratio of 9, and still be resistant to microbial contamination, because other drugs using parabens as preservatives use either much higher concentrations of parabens or much lower ratios of MP-PP or both, shown by a series of references: US 4,705,683:US 6,004,968; US2009/0137645; http://www.rxlist.com/levo-dromoran-drug.thm; and pp. 748-749 of Remington's Science and Practice of Pharmacy, 21st Ed. Applicant argues that those skilled in the pharmaceutical arts would not have been led to expect that a liquid pharmaceutical compostion comprising levocetirizine could be prepared with a total parabens concnentration of no more than 1.125 mg parabens/mL of solution and a MP:PP ratio of

9:1. This argument ignores the teachings of record. The fact that others use different ratios of MP/PP or higher amounts of a MP+PP combination or both does not refute the basis for the rejection.

The record indicates: Doron teaches the antibacterial effects of methyl and propyl paraben against Streptococcus sobrium, that antibacterial synergistic effect was found between several combinations of parabens (abstract); at 0.03% (about 0.3 mg/mL) propyl paraben (PP), with increasing amounts of methyl paraben, decreasing amounts of viable bacterial counts were demonstrated (p. 577, Figures 1-2), the ratios vary from 0.015:0.03 (1:2) MP:PP to 0.25:0.3 (8.33:1), or almost 9/1. At the highest ratio in both figures no bacterial counts were recorded (Figures 1-2; pp. 576-575, bridging paragraph). Additionally, MP had the largest antibacterial effect of the parabens tested (abstract). This article demonstrates that MP/PP ratio approaches 9/1, as claimed, rendering obvious the ratio 9/1, with the largest antibacterial effect at the highest ratio reported, rendering obvious the use of lower amounts of the two parabens at the 9/1 ratio. There is no comparative data on the record that compare the taught 8.33:1 ratio with the claimed 9/1 ratio, that might demonstrate the 9/1 ratio has some unexpected property over the Doron ratio taught.

The record further indicates Guilliland 2 teaches 4 combinations that have a MP/PP ratio of 8.6/1 for 0.12% MP + 0.014% PP; a ratio of 10/1 for 0.12% MP + 0.012% PP or 0.14% MP + 0.014% PP; and a ratio of 11.7/1 for 0.14% MP + 0.012% PP. These ratios bracket the claimed ratio of 9/1, rendering the ratio as an obvious variant of the taught ratios. With respect to the amounts, the use of lower amounts of a 9/1 ratio

is suggested by the largest antimicrobial activity taught by Doron taken together with the ratios of Guililand 2.

The record indicates Routledge teaches that a range of parabens, including methyl- and butylparaben, are weakly estrogenic, the suggestion is made that the safety in use of these chemicals should be reassessed, with particular attention being made to the estimation of the actual levels of systemic exposure of humans exposed to these chemicals, in order to assess the risk of exposure to parabens (abstract). This reference would have provided further motivation to minimize the levels of parabens to the minimum required in a formulation to provide some measure of antimicrobial growth reduction.

Applicant further argues the arguments previously made are incorporated by reference. All previously made arguments have been addressed in previous Office Actions.

Applicant argues Doron does not teach the use of parabens in combination with another pharmaceutical; therefore one cannot predict from Doron what effect parabens would have when used in combination. There are some expected results, such as greater antimicrobial efficacy at higher ratios of MP/PP, approaching the claimed 9/1 ratio. This permits less of the combination to be used to still achieve the same level of antimicrobial activity in a solution. This benefit would have been expected for a combination with a drug, also.

Applicant argues the data in Fig.1 of Doron is the antibacterial effect of immobilized S. sobrinus; that Doron states there is a stronger antibacterial effect of a

combination of parabens on immobilized bacteria compared to planktonic bacteria; that at least tow points follow: first, the difference in antibacterial effects of individual parabens v. combinations of parabens against immobilized and planktonic bacteria demonstrate a degree of unpredictability in extrapolating the antibacterial data to new situations. However, data are demonstrated for both types of bacteria (see Figures 1 & 2, where similar, but not quite the same level of activity is demonstrated for the combinations relevant to the instant claims.

Applicant further argues that, secondly, because combinations of parabens are more effective against immobilized bacteria than planktonic bacteria, the results reported in Figure 1 cannot be extrapolated to what one of ordinary skill in the art would expect in a liquid composition. This is precisely why comparative data is necessary to demonstrate a broad composition claim has unexpected results commensurate in scope with those claims. However, there is still data in Figure 2 that demonstrates zero growth at the highest MP/PP ratio for the planktonic bacteria.

Applicant argues the ratio of MP/PP at the selected data point is 0.5/1, far removed from the 9/1 ratio. The point is that the data demonstrate antimicrobial activity is present at this point, reduced levels of growth are demonstrated. Taken with the 9/1 ratio taught at the higher point, and the ratios of Guililand 2, with the recognition that some type of activity is present that in one sense is considered to be synergistic (see title), renders obvious a 9/1 ratio at the concentrations that would give 0.45 mg/ml or greater. MPEP 2141.03 (I) states:

> "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396. <

In the instant case the teachings of amounts and ratios of MP and PP in the combination of references render obvious claimed amounts and ratios.

Applicant argues Figure 1 of Doron shows that at the selected data point the viable bacteria count is greater than 35%, far greater that would be acceptable for a pharmaceutical product. This point has not been by evidence. There are conditions, such as when a product is bottled for single use in a sterile amount, that even less of the parabens would be required to add some antimicrobial pressure to the composition. The point is that there is some antimicrobial activity, even at this level, motivating the use of this level in compositions.

Applicant further argues that a complete antibacterial effect must be achieved; arguing antibacterial efficacy of a pharmaceutical composition must be continuously maintained over long periods of time and multiple exposures to bacterial; an acceptable pharmaceutical formulation must be completely bacterial resistant under such circumstances throughout the life of the product; that Fig. 1 of Doron shows that the only way to achieve complete eradication of bacteria would be for a 0.125 % MP

combined with 0.03% PP, for total parabens of 0.155% or 1.55 mg/mL. It is noted that the claims do not recite any such criteria for bacterial resistance, only the components of a composition are required, that have a pharmaceutical intended use. An antimicrobial effect may be achieved with a lower total amount of parabens, when there is, for example, a sterile solution; a refrigerated solution; or a solution containing a third preservative. Even the lowest level of 0.015 MP still demonstrates a reduction in viable bacterial counts; 0.03 and 0.06% also have reduced and nearly zero levels of viable bacteria in Figure 1. The 0.06% level MP, with 0.03 % PP (at 0.9 mg/ml total paraben), is clearly within the scope of the claimed 1.0 mg/ml total paraben amount of even claim 5. Compositions containing these levels of antimicrobial pressure on a solution would have motivated preparation of the claimed pharmaceutical compositions with total parabens in this range. However, the fact that there appears to be synergy at the higher ratios of MP/PP leads to an expectation that lower total paraben levels are likely to provide a better level of antimicrobial activity with a 9/1 MP/PP ratio.

Applicant argues Doron is evaluating various combinations of parabens to serve as antibacterial agents in the oral cavity, far different use from serving as a pharmaceutical preservative in a liquid composition as presently claimed. The data of Doron provides evidence that would motivate the use of MP and PP in the amounts and ratios of the instant claims, in compositions containing a drug, as claimed.

Applicant argues that "some" level of reduction in bacterial is not the standard for a pharmaceutical composition; the goal is substantially complete eradication of bacteria, to protect that pharmaceutical composition from bacterial contamination; that the Action

provides no scientific basis or reasoning why altering the MP/PP ratio of Doron to that recited in the present claims would be expected to yield a complete antibacterial result. Complete antibacterial result is not a requirement of the instant claims. The reduction of microbial levels would provide a benefit, in some circumstances, such as single doses of a drug that are sealed under sterile conditions, or for a solution intended to be stored in a refrigerator, or when an additional stabilizer is also present.

Applicant argues one skilled in the art upon reading Doron would have no reason to recognize that the presence of levocetirizine in the claimed composition unexpectedly allows for the use of lower concentration of parabens when the parabens are used in the claimed ratio while still achieving essentially complete eradication. This argument is not based on a claim limitation, but on an unexpected result disclosed. It has been previously noted that there is comparative data present in the specification that demonstrates the argued properties. However, the data of the specification are not commensurate in scope with the claims for any claim under examination, which utilize open language, permitting even other antimicrobial agents, some of which are specifically recited in withdrawn claims. The amounts of the tested compositions are not limited to the amounts of the claimed components in any of the claims under examination; the solutions tested all contain additional ingredients at specific amounts (as disclosed in Table 4) that are not recited in any of the claims. MPEP 716.02 (d) states:

716.02(d) Unexpected Results Commensurate in Scope With Claimed Invention [R-2]

> Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)

In the instant case, there are specific components present in the compositions tested; the claims are much broader, using open language, and not reciting all of the components in the tested compositions, let along not reciting them in the amounts they were tested. The claims permit, even withdrawn claims recite, the presence of additional antimicrobial stabilizers. The presence of such a compound would change the level at which antimicrobial activity is present. Applicant is invited to present claims limited to the components of the compositions actually tested in the amounts tested, for which the presence of levoceritizine resulted in lower levels of microbial growth. Favorable consideration would be given to claims so limited.

Applicant argues as to Routledge's incentive to lower levels of parabens due to their estrogenic activity, that fails where such lower levels are shown in Doron to be ineffective. The levels in Doron are not ineffective; they are less effective. Applicant further argues that Routledge demonstrates a long-felt need for a pharmaceutical composition that could achieve substantially complete eradication of bacteria while

minimizing the estrogenic effect of the preservatives in the composition; that it was heretofore unrecognized that such a need could be met by using such a small quantity of parabens at the 9:1 MP/PP ratio in a levocetirizine composition.

With respect to the argument that the claimed subject matter solved a problem that was long standing in the art, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04.

Conclusion

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1628